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published in
British Journal of Sports Medicine
2015

DOI (link to publisher)
10.1136/bjsports-2015-095476

Central pain processing is altered in people with Achilles tendinopathy

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Accepted 23 November 2015

ABSTRACT

Background Tendinopathy is often a chronic condition. The mechanisms behind persistent tendon pain are not yet fully understood. It is unknown whether, similar to other persistent pain states, central pain mechanisms contribute to ongoing tendon pain.

Aim We investigated the presence of altered central pain processing in Achilles tendinopathy by assessing the conditioned pain modulation (CPM) effect in people with and without Achilles tendinopathy.

Methods 20 people with Achilles tendinopathy and 23 healthy volunteers participated in this cross-sectional study. CPM was assessed by the cold pressor test. The pressure pain threshold (PPT) was recorded over the Achilles tendon before and during immersion of the participant's hand into cold water. The CPM effect was quantified as the absolute difference in PPT before and during the cold pressor test.

Results An increase in PPT was observed in the Achilles tendinopathy and control group during the cold pressor test ($p<0.001$). However, the CPM effect was stronger in the control group (mean difference=160.5 kPa, SD=84.9 kPa) compared to the Achilles tendinopathy group (mean difference=36.4 kPa, SD=68.1 kPa; $p<0.001$).

Summary We report a reduced conditioned pain modulation effect in people with Achilles tendinopathy compared to people without Achilles tendinopathy. A reduced conditioned pain modulation effect reflects altered central pain processing which is believed to contribute to the persistence of pain in other conditions. Altered central pain processing may also be an important factor in persistent tendon pain that has traditionally been regarded to be dominated by peripheral mechanisms.

INTRODUCTION

Tendinopathy is a generic term used to describe tendon pathologies that typically manifest in pain, swelling and dysfunction.[1] Despite best available management, tendon pain often becomes chronic.[2 3] Furthermore, the mechanisms underlying persistent tendon pain are not yet fully understood.

Tendinopathy has traditionally been viewed as a peripheral disorder confined to the tendon itself. However, recent evidence suggests other possible contributors to the persistence of tendon pain.[4–8] Many chronic pain conditions share a number of typical features, such as hyperalgesia/allodynia,[9 10] widespread pain[11 12] and reduced endogenous pain modulation.[10 13] In line with these presentations, various tendinopathies are characterised by mechanical hyperalgesia,[14 15] pinprick allodynia and increased vibration disappearance thresholds.[16] In contrast, widespread pain is not a common clinical presentation of tendinopathy.[5 17 18] Yet, bilateral symptoms (including sensory and motor deficits) are often reported.[3 6 14] Up to now, altered central pain modulation (CPM) mechanisms have received little research attention in people with tendon pathology.

Endogenous pain modulation is governed by the central nervous system via facilitatory and inhibitory mechanisms. CPM testing paradigms are used to examine the efficacy of descending pain modulatory pathways.[19] In this experimental approach, the application of a noxious 'conditioning' stimulus typically results in pain inhibition for a subsequent testing stimulus. CPM is, therefore, quantified as the change in the intensity necessary to evoke pain (or pain intensity) of the testing stimulus before and during the application of the conditioning stimulus.[20] Persistent pain may reflect a possible dysfunction in the inhibitory circuits[21] which has been evident in a plethora of chronic pain conditions such as fibromyalgia,[22] irritable bowel syndrome,[23] pancreatitis,[24] tension type headache,[25] temporomandibular disorders,[23] osteoarthritis[26] and low back pain.[27] Whether chronic tendon pain is associated with similar deficits in central pain modulatory mechanisms is yet to be investigated. Therefore, the aim of this study was to examine the efficacy of CPM in people with chronic Achilles tendinopathy compared to healthy individuals.

METHODS

Study design

A cross-sectional study.

Participants

People with and without Achilles tendinopathy were eligible to participate. Participants were recruited via print and social media advertisements from October 2014 to February 2015 they had to be actively engaged in running activities at the period of testing. All volunteers with pain over the Achilles tendon region underwent a patient interview and clinical examination. The diagnostic criteria for Achilles tendinopathy included a characteristic history of activity-related pain and tenderness on tendon palpation.[15 28] Participants with Achilles tendinopathy were included if they presented with pain in the Achilles tendon for at least 3 months prior to testing. Participants with any other medical condition or musculoskeletal disorder in the preceding 6 months that lasted for more than 1 week or for which treatment was sought were excluded. Further exclusion criteria were the presence of systemic disorders,

To cite: Tompra N, van Dieën JH, Coppieters MW. *Br J Sports Med* Published Online First: [*please include* Day Month Year] doi:10.1136/bjsports-2015-095476

cardiovascular or neurological problems, fibromyalgia and any medication usage.

Thirty volunteers with pain over the Achilles tendinopathy region agreed to participate, but 10 did not meet the criteria (9 were excluded because they did not have Achilles tendinopathy; 1 patient with Achilles tendinopathy experienced symptoms for less than 3 months). In addition, 26 symptom-free runners without Achilles tendinopathy were recruited from the same population, using the same recruitment strategies.

All participants completed the Victorian Institute of Sports Assessment—Achilles Questionnaire (VISA-A)[29] and the 21-item activities of daily living (ADL) subscale of the Foot and Ankle Ability Measure (FAAM).[30] Additionally, the participants from the Achilles tendinopathy group were asked to draw the areas where they experienced pain on a lower limb chart.[28]

The study was approved by the local ethics committee of the Department of Human Movement Sciences of VU University, Amsterdam, the Netherlands (Reference: ECB 2014–58). It was conducted according to the Declaration of Helsinki and all participants signed an informed consent prior to their participation.

CPM testing protocol

To explore CPM, the cold pressor test was used as the conditioning stimulus and the pressure pain threshold (PPT) as the test stimulus.[19 20] Participants submerged their hand contralateral to their affected ankle (or the most affected in case of bilateral Achilles tendinopathy) in a container with cold water (approximately 9° Celsius). Healthy volunteers immersed their dominant hand. Continuous circulation of the water in the container was implemented in order to prevent an increase in temperature around the hand.[31] The water temperature was monitored by a thermometer with a digital display (resolution: 0.1°C). The participants placed their hand in the water up to the level of the wrist and they were instructed to keep their fingers spread. They were asked to rate their perceived hand pain on a 0 ('no pain') to 10 ('worst imaginable pain') numerical pain rating scale (NPRS). The CPM assessment began as soon as a score of 5 was reached. When required, ice was added to the water in order to maintain a minimum pain score of 4 on the NPRS during the experiment.

The PPT measurements were performed using a digital algometer (Type II, Somedic AB, Stockholm, Sweden). The participants were placed prone on a treatment plinth with their feet against the wall ensuring an ankle position of 0°. The assessment site was the most painful location of the Achilles tendon as determined by manual palpation.[32] For the control group, the point of pressure application was the mid-portion of the Achilles tendon (approximately 2–3 cm proximal to the insertion). The probe was placed perpendicular to the skin and the pressure was applied through a 1 cm^2 rubber plate at a constant rate of 40 kPa/s. The participants were instructed to press a button as soon as the applied pressure was perceived as painful.

Three consecutive trials with 30 s intervals were performed before and during the application of the conditioning stimulus. If the difference in consecutive PPTs reached more than 100 kPa, the procedure was repeated until three PPTs would differ by less than 100 kPa within a maximum of five measurements in total. The mean score of the three trials with the least variance was calculated and used for further analysis. This method showed excellent intra-rater reliability (Intraclass Correlation Coefficient ($ICC_{(2,1)}$): 0.96; 95% CI 0.88 to 0.99; SE of Measurement (SEM): 8.74 kPa; Minimum Detectable Change (MDC): 24.2 kPa) in a prior pilot study on 12 healthy volunteers.

To familiarise the participants with the PPT measurements, PPTs were performed over the thenar eminence of the dominant hand and over the Achilles tendon contralateral to the tested ankle before the actual experiment started. All experiments took place in the Vrije University of Amsterdam, Amsterdam, the Netherlands.

Statistical analysis

The characteristics of the group with and without Achilles tendinopathy were compared with independent t tests, given a normal distribution of the data. Independent t tests were also used to examine potential differences between groups for the water temperature and the intensity of the induced hand pain during cold pressor test. For ordinal or non-normally distributed data, the equivalent non-parametric test (Mann–Whitney U) was performed. Normality was checked by visual inspection of the q–q plot, the box plot of the data, and a Shapiro-Wilks test.

To determine whether there was a difference in CPM responses between the Achilles tendinopathy and the control group, PPTs were investigated in a 2×2 (Time (before and during the cold pressor test)×Group (Achilles tendinopathy and control group)) repeated-measures analysis of variance (ANOVA). The normality and homogeneity of variance of the data were examined prior to the test. There were no violations of these assumptions. Any Group×Time interaction was clarified by examining the difference in the CPM effect (quantified as the difference in PPT values before and during cold pressor test) between the groups with an independent t test.

Given a non-normal distribution, Spearman correlation coefficients (r) were calculated to explore whether the pain severity (NPRS), symptom duration, functional limitation (FAAM) and Achilles tendinopathy severity (VISA-A) were related to the CPM response in the Achilles tendinopathy group.

RESULTS

Three healthy participants were excluded from the analysis (two participants did not maintain the minimum required score of 4 on the NPRS during the cold pressor test; one participant reported no pain during pressure application over the Achilles tendon). Figure 1 visualises the pain location as reported by the Achilles tendinopathy group. The characteristics of all participants who completed the experiment are shown in table 1. The Achilles tendinopathy group was on an average older than the control group (mean difference 6.8 years), yet the difference did not reach statistical significance (95% CI (−14.68 to 1.18)). The amount of running and cross-training per week was not significantly different between the two groups. The outcomes of FAAM and VISA-A were significantly lower in patients compared to healthy participants. The PPT on the thenar eminence did not differ significantly between the groups (mean difference=35.1, t(41)=1, p=0.33, 95% CI (−37.3 to 107.6)).

Conditioned pain modulation

During the cold pressor test, the water temperature was similar for both the Achilles tendinopathy and control group (approximately 9°C). The level of induced hand pain was slightly higher for people with Achilles tendinopathy than for healthy participants, yet the difference was not statistically significant (mean difference=0.7, 95% CI (−1.5 to 0.2); table 2).

There was a significant main effect for time ($F(1,41)=68.93$, $p<0.001$, $\eta_r^2 = 0.63$) and an interaction with the group ($F(1,41)=27.36$, $p<0.001$, $\eta_r^2 = 0.4$), indicating that the

change in PPT during the cold pressor test was different for both groups. The CPM effect for the Achilles tendinopathy group was significantly lower than for the control group (mean difference=124.1 kPa, t(41)=5.2, 95% CI (76.2 to 192)). The CPM responses are illustrated in table 2.

Correlations

No significant correlations between pain severity experienced the week prior to the test (NPRS) (r=0.19; p=0.427), duration of symptoms (r=−0.41; p=0.07), FAAM score (r=0.22; p=0.35) or the VISA-A score (r=0.02; p=0.95) and the CPM effect were identified.

DISCUSSION

We investigated differences in central pain processing between people with Achilles tendinopathy and healthy individuals. There was a significantly smaller CPM effect exhibited during the cold pressor test in the Achilles tendinopathy group compared to the control group. This indicates that central pain modulatory processes are altered in people with Achilles tendinopathy.

CPM and chronic pain

CPM is a phenomenon that reflects the activity of the descending pain modulation system.[20 33] A deficit in its function has been reported in a variety of clinical conditions associated with chronic pain.[34–36] The results of this study reveal a reduced CPM effect in people with Achilles tendinopathy. As no previous studies have investigated CPM in a tendinopathy, comparisons with the present study are not yet possible. Nonetheless, our findings provide evidence that people with Achilles tendinopathy share similar changes in central pain modulation mechanisms as do chronic pain patients with fibromyalgia,[22 37] irritable bowel syndrome,[23 38 39] temporomandibular disorders,[23 40] whiplash-associated disorders,[41 42] tension type headache,[25 43 44] osteoarthritis[26 45] and low back pain.[27] Such changes have been suggested to contribute to the development of central sensitisation[9 46–48] and chronicity of pain.[49 50] Indeed, most of the aforementioned conditions are expected to exhibit signs of central sensitisation.[11 26 51–58] Whether this is also the case in people with Achilles tendinopathy remains to be investigated in future research. Nonetheless, the reduced CPM effect in people with Achilles tendinopathy, as observed in this study, suggests a role of altered central pain mechanisms and may reveal a factor contributing to chronic tendon pain.

It is a novel and interesting finding that CPM is reduced in people with Achilles tendinopathy. Tendinopathy seems a particular chronic pain state in which tendon pain is provoked

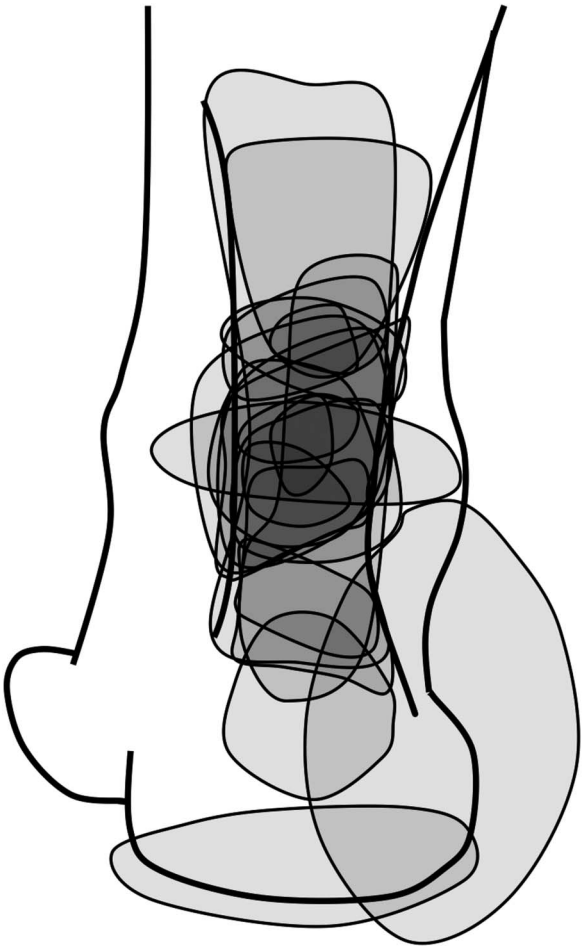

Figure 1 Area of pain for the people with Achilles tendinopathy. Darker colours represent a larger number of participants reporting pain the corresponding area. Regardless of whether the left or right Achilles tendon was affected, the locations are summarised on a diagram of the right ankle (ie, locations on the left side were mirrored).

Table 1 Characteristics (mean (SD)) of the Achilles tendinopathy (Achilles tendinopathy) and the control group

	Control (N=23)	Achilles tendinopathy (N=20)	p Value
Age (years)	36.2 (12.3)	42.9 (13.5)	0.09
Gender (male/female)	16/7	16/4	–
Body mass index	21.9 (2.5)	23.4 (2.7)	0.11
Symptom duration (months)	NA	21.8 (26.1)	–
Side of symptoms (unilateral/bilateral)	NA	11/9	–
NRPS (past week)	NA	3.7 (1.9)	–
VISA-A questionnaire	99.8 (0.9)	71.6 (15.8)	<0.001
FAAM questionnaire	99.8 (0.5)	90.5 (10.7)	<0.001
Running (km/week)*	30.0 (33)	27.5 (45)	0.11
Cross-training (hours/week)	2.4 (2.6)	1.7 (1.7)	0.51
PPT thenar (kPa)	372.5 (107.7)	337.4 (127.5)	0.33

FAAM, Functional Ankle Ability Measure; Km, kilometres; NA, not applicable; NPRS, Numerical Pain Rating Scale; PPT, pain pressure threshold; VISA-A, Victorian Institute of Sport Assessment-Achilles.
*Data are presented as Median (IQR).

Table 2 Cold pressor test (mean (SD))

	Control (N=23)	Achilles tendinopathy (N=20)	p Values*
Achilles tendon PPT (kPa)†			
Before cold pressor test	671.4 (215.7)	253 (80.5)	<0.001
During cold pressor test	831.9 (213.3)	289.4 (114.3)	<0.001
CPM effect (kPa)	160.5 (84.9)	36.4 (68.1)	<0.001
Water temperature (°C)	9.0 (0.9)	9.1 (0.8)	0.73
NPRS during cold pressor test	6.2 (1.3)	6.9 (1.6)	0.15

*p Values correspond to independent t tests.
†Contralateral to the dominant hand for the control group and the (most) affected for the Achilles tendinopathy group.
°C, degrees Celsius; CPM, conditioned pain modulation; kPa, kilopascal; NRPS, Numerical Pain Rating Scale.

during loading and subsides once the load has been removed.[5] Moreover, unlike other chronic pain conditions, Achilles tendinopathy is not accompanied by great limitations in physical functioning or ADLs. Particularly in the recruited Achilles tendinopathy group, despite the long mean symptom duration (≈2 years), pain intensity was moderate (≈4 on the NPRS) and the activity level similar to the control group. In contrast to what has been reported so far in the literature,[59] in the present study the CPM effect was not correlated with the functional ability or the activity level of the patient group.

Central versus local mechanisms

Of particular importance in interpreting the altered CPM response may be the net influences of local and central pain mechanisms. It has been argued that local neural and inflammatory processes may conceal endogenous analgesia.[60 61] Sustained peripheral nociceptive activity from the tendon tissue (see Rio *et al*[5] for a review) may sensitise nociceptive neurons in the dorsal horn of the spinal cord[9] increasing their excitability, thus counteracting the effects of descending inhibition. In two studies in people with knee and hip osteoarthritis, the CPM effect was weakened before but not after surgery, implying that the reduced CPM was the result of ongoing nociceptive activity.[45 62] Although inflammatory mediators are not always expressed in tendinopathy,[5 63] it is possible that the observed reduction in the CPM effect is the manifestation of both peripheral and central pain mechanisms rather than central changes alone.

Methodological variability with regards to CPM testing location has been noted in the literature. Attenuated CPM in conditions such as irritable bowel syndrome, tension type headache and pancreatitis has been demonstrated at pain-free sites,[23–25 38] whereas in temporomandibular disorders and osteoarthritis reductions were found only at the painful or intrasegmental areas.[26 40 45] The syllogism behind testing CPM at a pain-free or intact tissue is based on the fact that CPM is regarded as a systemic rather than a localised phenomenon.[60] Hence, a CPM reduction exhibited in a pain-free area would be indicative of a limitation of an individual's endogenous analgesic capacity. Moreover, as speculated above, a reduction in CPM in the affected tissue could be conveyed by both peripheral and central pain mechanisms. On the other hand, the absence of a CPM reduction in an area remote to the painful site does not exclude a possible contribution of central pain modulatory processes to the ongoing pain. The idea that a change in descending modulation will be evident in any area remote to the injured or painful site features a static nature in a rather dynamic phenomenon.[36] This raises questions regarding the choice of the most appropriate testing location which would be anatomically close to—yet sufficiently remote from—the painful region. The design of the present study did not allow for a comparison of the CPM at the painful versus a pain-free site. Comparison of the CPM effect as elicited from affected versus unaffected tissues would have a great potential in further enhancing our understanding of tendon pain pathophysiology and warrants future research.

Is weaker conditioned pain modulation 'dysfunctional'?

Another point that merits attention is the label 'dysfunctional' that is given to CPM when found to be different between patient and healthy groups. Rationalising CPM teleologically by the speculative but widely accepted notion that pain acts as a warning system for danger or threat, the reduced CPM response pattern seen in patient populations might reflect an adaptive mechanism with the purpose to protect the painful area. For such an adaptation to be functional, the assumption that a threat is implied to the body is required. It is possible that the reduced CPM effect in the Achilles tendinopathy group, as observed in this study, is the expression of a dynamic and flexible pain modulation process in the presence of increased afferent nociceptive input warning for tissue damage. However, this view is confronted by the common disassociation of tissue damage and pain.[64–67]

CONCLUSION

Although the pain in tendinopathy is generally considered to be driven by peripheral mechanisms, the findings of this study reveal that people with Achilles tendinopathy modulate pain centrally in a different way than healthy people. Such differences are evident in a variety of chronic pain conditions and have been suggested to contribute to the chronicity of pain. Thus, the reduced CPM as observed in people with Achilles tendinopathy may promote ongoing tendon pain.

What are the findings?

- Pressure pain threshold testing over the Achilles tendon revealed that the conditioned pain modulation effect is reduced in people with Achilles tendinopathy.
- The findings indicate that besides peripheral mechanisms, altered central pain processing also plays a role in persistent Achilles tendinopathy.
- The reduction in conditioned pain modulation in people with Achilles tendinopathy was not correlated with the severity of Achilles tendinopathy (VISA-A), functional limitations (FAAM), and activity levels (amount of running).

How might it impact on clinical practice in the future?

- If altered central pain modulation in people with Achilles tendinopathy can be substantiated in future studies, the clinical examination for people with Achilles tendinopathy might have to incorporate assessment techniques to identify all relevant contributing pain mechanisms.
- If future research confirms altered central pain modulation in people with Achilles tendinopathy, it would be logical to explore drug therapy and treatment modalities that target the central nervous system in people with Achilles tendinopathy.
- Considering the presence of altered conditioned pain modulation effects in people with Achilles tendinopathy, similar findings in patients with chronic and widespread pain conditions, such as fibromyalgia and chronic fatigue syndrome, may need to be reinterpreted.

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Contributors NT was responsible for the acquisition and analysis of the data, and drafting of the work All authors contributed substantially to the conception and design of the work, and the interpretation of the data. All authors revised the work critically for intellectual integrity and provided final approval for the version to be published.

Competing interests None declared.

Ethics approval Ethics committee of the Department of Human Movement Sciences of VU University Amsterdam, The Netherlands (Reference: ECB 2014-58).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Raw data can be shared for research purposes on request.

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Br J Sports Med published online December 23, 2015